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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,686	11/28/2001	Klaus During	03528.0133.PCUS00	7122

7590 06/03/2004

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EXAMINER	
HELMER, GEORGIA L	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,686	DURING ET AL.	
	Examiner	Art Unit	
	Georgia L. Helmer	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 16-18* is/are pending in the application.

4a) Of the above claim(s) *3,5 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-8,10-14 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The Office acknowledges receipt of Applicant's restriction election, dated 18 March 2004. Applicant has elected without traverse Group I, claims 1, 2, 4, 6-8, 10-14, and 16-18, drawn to a method of obtaining a desired protein from a transgenic host organism by modifying the gas phase surrounding the organism and the transgenic host organism.

2. Claims 1-14 and 16-18 are pending; claims 3, 5, and 9 are withdrawn as being drawn to nonelected invention(s). Claims 1, 2, 4, 6-8, 10-14, and 16-18 and are examined in the instant action.

Claim Rejections - 35 USC § 112 Enablement

3. Following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 6-8, 10-14, and 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of

obtaining an scFv antibody protein from a transgenic potato, wherein the transgenic potato contains a scFv antibody protein coding sequence under the control of the GapC4 promoter, the GapC4 promoter being inducible by anaerobic conditions, harvesting pieces of potato and then exposing them to anaerobic conditions for a period of time of 40 hours, does not reasonably provide enablement for the broad scope of the claims. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)).

The breadth of the claims: The claims are drawn to a method of obtaining a desired protein from a transgenic host organism wherein the expression of the gene coding for this protein does not occur until the host organism has been harvested. wherein the transgenic host organism contains the gene coding for the desired protein such that it is only expressed in the presence of a chemical inductor, and contacting with the inductor takes place via the phase surrounding the host organism after the host organism has been harvested, wherein the phase surrounding the host organism is a gas phase or a liquid phase, wherein the contacting step comprising modifying the gas phase surrounding the host organism, where modifying the gas phase is deoxidizing the gas phase and the promoter is a promoter inactive under aerobic conditions, wherein the gene coding for the desired protein is functionally linked with an inducible promoter, and where the promoter is the GapC4 promoter, and wherein the expression of the gene coding for the desired protein is induced by compensating the functional inhibition of the transcription and/or translation. The claims are also drawn to the method wherein the gene coding for the desired protein is functionally linked with a promoter, so that between the promoter and the gene, a nucleic acid is inserted such that it prevents the transcription and/or translation of the gene, and it can be excised after the induction, which results in the expression of the gene, wherein the nucleic acid is one which can be excised by an inducible recombinase, where the excisable nucleic acid and the

recombinase are constituents of the recombinase-LBD system, where the transgenic organism is useful plant, the plant being wheat, barley, corn, sugar beet, sugarcane, potato, brassicaceae, a leguminous plant or tobacco. The claims are also drawn to a host organism which contains the gene coding for the desired protein such that it is only expressed in the presence of a chemical inductor. The claims are broadly drawn to all host organisms including bacteria, virus, algae and mosses, fungi, all animals including insects and mammals and elephants, and all plants including trees and cactus, all proteins, any chemical inducer, and any recombinase.

The state of the art and the unpredictability thereof: The state of the art of chemical control of gene expression is unpredictable (Gatz, Chemical Control of Gene Expression, Annu. Rev. Plant Physiol. Plant Mol. Biol., vol. 48, pages 89-108, 1997, see p. 99, 1st full ¶, and 104, 2nd full ¶). The state of the art of post harvest production systems for production of desired proteins in plants is that the systems which have been described are systems based on the wounding of plant material, which is a system which is inducible/induced in both pre- and post-harvest conditions (specification p. 2, 1st full ¶).

Guidance in the specification: Applicant claims all host organisms, but Applicant gives no guidance for any organism other than plants, specifically the dicot potato plant. Applicant claims all inducible promoters, but teaches only the maize GapC4 promoter, which is induced by anaerobic conditions, and functionally inactive under aerobic conditions. Applicant claims all chemical inductors, the presence of which is required

for expression of the desired protein. Applicant teaches only the presence of aerobic conditions (lack of oxygen) as being the chemical inductor.

No single expression system exists for all host organisms, including bacteria, viruses, fungi, animals and plants.

Working Examples: Applicant teaches a method of obtaining scFv antibody protein from a transgenic potato plant, where the transgenic construct uses the maize anaerobically inducible CapC4 promoter operatively linked to the cDNA which codes for an scFv antibody protein, where tissue is harvested and then is induced by treatment with anaerobic conditions for 40 hours (Example 1, pages 14-16, of the specification).

No examples of use of inducible recombinase systems are taught in the specification. Example 2, p. 16-18, is titled Recombination–mediated post-harvest production in transgenic potatoes. However, the description of this work is so thin that the Examiner is unable to evaluate what, if anything, is enabled.

Experimentation required: Undue trial and error experimentation would be required to determine which host organism would be suitable for post harvest protein production, as "harvest" is typically associated with crop plants and plant parts, not other host organisms, and which host organism would be capable of enhanced or de novo protein production after having been harvested, excised or removed, because the normal expectation is that once removed from the "parent", tissue begins degradation by apoptotic and senescence processes which degrade proteins, and does not synthesize new or more proteins. Having determined a suitable host organism, the post harvest production system itself would have to be determined; if an inducible system,

what kinds of induction signals would be appropriate for the host and the harvested tissue. This experimentation would be manifold and would include determining which genetic components would be suitable for that specific host system chosen, including what induction system, of which there are many, such as wound-induction, chemical induction, hormone induction (ethylene), temperature induction (heat shock for example), osmotic induction (salt stress) , light induction (photosynthesis), time period induction (circadian), and aerobic status (aerobic conditions v. anaerobic conditions). Multitudinous experimentation would be necessary, having determined the host, and the induction system, to determine specific appropriate inducers, if chemical, which chemical(s) at what concentration, for what time duration, at what temperature, and how is the chemical provided to all the cells of the tissue, similarly for each induction system. Then a plethora of experiments would be necessary, having determined all the above information, to determine which genetic regulatory system would function as desired, for example if a hormone induced system, what genetic regulatory systems are available, such as ethylene-responsive prompters/regulatory sequences are known and characterized and could they function as desired? A myriad of experimentation involving cascades of experiments dependent one upon the other would be required, to determine what host, what induction system, how to manipulate that system appropriately, what genetics components are available and would work.

Applicant must provide sufficient guidance to address these issues. Without such guidance the experimentation required would not be routine, but would be undue.

This would impose a burden on the skilled artesian, without a reasonable expectation of success.

In view of the breadth of the claims (all host organisms including bacteria, virus, algae, mosses, fungi, all animals including insects and mammals and elephants, and all plants including trees and cactus, all proteins, all chemical inducers, and all recombinases), the nature of the invention, the unpredictability of the art, the lack of guidance in the specification, undue trial and error experimentations would be required to enable the invention as commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, 4, 6-8, 10 and 16-18 are rejected under 35 U.S.C. 102(e) over US 6,194,201 B1 issued 27 February 2001, with a 102(e) date of 27 October 1998.

US 6,194,201 B1 (hereafter '201) teaches a method of obtaining a desired protein, where the protein is a T4 virus lysozyme enzyme (column 3, lines 55-58) from a transgenic potato plant, wherein the expression of the gene coding for this protein does not occur until the host organism has been harvested because the conditions for inducing the maize Gap4C promoter driving the T4 coding sequence are anaerobia (no/low oxygen) and are not applied until after harvest, where the lack of oxygen (presence of CO2) is a chemical inductor, and contacting with the inductor takes place via the gas phase (column 3, lines 59-61) surrounding the host organism after the host organism has been harvested, where modifying the gas phase is deoxidizing the gas phase (column 3, lines 59-61) and the promoter is the maize GapC4 promoter, which is a promoter inactive under aerobic conditions and activity is induced by anaerobic conditions, and wherein the expression of the gene coding for the desired protein is induced by compensating the functional inhibition of the transcription and/or translation.

RE: Claim 10. The language "induced by compensating the functional inhibition of the transcription and/or translation" is unclear and ambiguous. Therefore the Examiner interprets these terms to mean turning expression "on" from an "off" state, which is what happens when anaerobic conditions induce the GapC4 promoter to express the Glucuronidase protein.

The '201 patent also teaches modifying the gas phase surrounding the transgenic plant tissue by deoxidizing the gas phase (column 3, lines 59-61), the gene

coding for the desired protein, Glucuronidase protein, is functionally linked with the inducible promoter , the maize GapC4 promoter. The '201 patent teaches the transgenic organism being a useful plant, the plant being wheat, barley, corn, sugar beet, sugarcane, potato, brassicaceae, a leguminous plant or tobacco (column 2, lines 12-14).

The language "induced by compensating the functional inhibition of the transcription and/or translation" is unclear and ambiguous. Therefore the Examiner interprets these terms to mean turning expression "on" from an "off" state, which is how anaerobic conditions in the gas phase induce expression of the Gap4C promoter.

Accordingly US 6,194,201 anticipates the claimed invention.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless –**
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6-8, 10 and 16-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Kohler et. al. (A promoter for strong and ubiquitous anaerobic gene expression in tobacco, The Plant Journal, vol. 10 , pages 175-183, 1996).

Kohler et. al. teaches a method of obtaining a desired protein, where the protein is a Glucuronidase enzyme (p. 182, 6th full ¶) from a transgenic tobacco plant, wherein the expression of the gene coding for this protein does not occur until the host organism has been harvested because the conditions for inducing the maize Gap4C promoter

driving the Glucuronidase coding sequence are anaerobia (no/low oxygen) and are not applied until after harvest, where the lack of oxygen (presence of CO2) is a chemical inductor, and contacting with the inductor takes place via the gas phase (p. 182, 5th full ¶) surrounding the host organism after the host organism has been harvested, where modifying the gas phase is deoxidizing the gas phase (p. 182, 5th full ¶) and the promoter is the maize GapC4 promoter, which is a promoter inactive under aerobic conditions and activity is induced by anaerobic conditions, and wherein the expression of the gene coding for the desired protein is induced by compensating the functional inhibition of the transcription and/or translation.

RE: Claim 10. The language "induced by compensating the functional inhibition of the transcription and/or translation" is unclear and ambiguous. Therefore the Examiner interprets these terms to mean turning expression "on" from an "off" state, which is what happens when anaerobic conditions induce the GapC4 promoter to express the Glucuronidase protein.

Kohler et. al. also teaches modifying the gas phase surrounding the transgenic plant tissue by deoxidizing the gas phase (p. 182, 5th full ¶), the gene coding for the desired protein, Glucuronidase enzyme protein, is functionally linked with the inducible promoter , the maize GapC4 promoter. Kohler et. al. also teach the transgenic organism being a useful plant, the plant being wheat, barley, corn, sugar beet, sugarcane, potato, brassicaceae, a leguminous plant or tobacco (p. 182, 4th full ¶).

Accordingly Kohler anticipates the claimed invention.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 2, 4, 6-8, 10-14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohler et. al. as applied to claims 1, 2, 4, 6-8, 10 and 16-18 above, and further in view of WO 95/00555 (5 January 1995).

Kohler et. al. do not teach a method using a LBD (ligand binding domain) recombinase system.

WO 95/00555 (hereafter '555) teaches a method using a LBD (ligand binding domain) recombinase system (p. 3, 1st and 2nd full ¶s) where inducible recombinase is FLP recombinase translationally fused to the Estrogen LDB and where the recombinase is not active until the Estrogen LBD is bound to its receptor in the nucleus (Figure 1B).

WO 95/00555 provides motivations to combine use of the LBD-recombinase system with the method of obtaining a desired protein of Kohler et. al. (Abstract) saying that the LBD-recombinase system provides a practical means to regulate recombinase in cells and organisms.

Given the recognition of one of ordinary skill in the art of the value of using the claimed invention in harvested plants, one of ordinary skill in the art would have been motivated to use Kohler et. al.'s anaerobic gene expression in post-harvest tobacco, in

combination with the LBD recombinase system of WO 95/00555 in order to regulate and activate the availability of Kohler et. al.'s anaerobic gene expression to produce glucuronidase in post-harvest tobacco. Thus the claimed invention would have been prima facie obvious as a whole to one of ordinary skill in the art at the time it was made. Accordingly, the claimed invention is prima facie obvious in view of the prior art.

RE: Claim 14. The language "induced by compensating the functional inhibition of the transcription and/or translation" is unclear and ambiguous. Therefore the Examiner interprets these terms to mean turning expression "on" from an "off" state, which is what happens when anaerobic conditions induce the GapC4 promoter to express the Glucuronidase protein.

Remarks

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Georgia L. Helmer whose telephone number is 571-272-0976. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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June 1, 2004

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